

State of the art : “Diastology” research 1998

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Abstract : The performance of the left ventricle (LV) during diastole is defined by the pressure-volume relationship. Consequently, noninvasive techniques have been limited in the evaluation of diastolic function by their inability to evaluate intracardiac pressure, particularly LV filling pressure and end-diastolic pressure. Abnormalities of LV diastolic function play a major role in producing the clinical signs and symptoms of heart failure. Previous studies have demonstrated that the transmitral flow (TMF), pulmonary venous flow (PVF) and left atrial appendage flow (LAAF) velocity patterns determined by pulsed Doppler echocardiography are useful parameters for evaluating left atrial (LA) and LV hemodynamic events. However, these variables are influenced by loading conditions, particularly preload. Furthermore, it has become increasingly clear that abnormalities of LV diastolic function, such as relaxation and filling, can be assessed precisely using color Doppler M-mode echocardiography and pulsed tissue Doppler imaging irrespective of preload. This review presents a clinical approach to understanding the hemodynamic abnormalities of the LA and LV in a variety of cardiac diseases using these new modalities. In addition, the limitations of these techniques are discussed. *J. Med. Invest.* 45 : 9-25, 1998

Key words : LV diastolic function, pulsed Doppler echocardiography, pulsed tissue Doppler imaging

INTRODUCTION

It has been reported that as many as one third of patients evaluated for congestive heart failure may have a normal left ventricular (LV) ejection fraction, which suggests that diastolic dysfunction is the major pathophysiologic abnormality in these patients (1-4). It has become increasingly clear that abnormal diastolic function plays a major role in producing the signs and symptoms in patients presenting with heart failure (5, 6). Therefore, the term “diastology” is currently used to refer to the characterization of LV relaxation and filling dynamics.

Cardiac catheterization is the standard technique for direct measurement of LV filling pressure and the rate of LV relaxation. However, catheterization is not practical for routine clinical application or serial

examinations because of its invasive approach. Pulsed Doppler echocardiography is a relatively new, noninvasive and easily performed technique that allows measurement of blood flow velocities across the mitral valve (transmitral flow : TMF) (7, 8), from the pulmonary veins to the left atrium (LA) (pulmonary venous flow : PVF) (9,10), and from the left atrial appendage to the LA main chamber (left atrial appendage flow : LAAF) (11, 12). The many advantages of this technique make it a potentially valuable tool for the evaluation of LA and LV hemodynamic abnormalities. Furthermore, in recent years, tissue Doppler imaging has been developed in which large Doppler signals obtained from the LV wall can be selectively displayed as a color or pulsed Doppler image by eliminating small Doppler signals produced by the blood flow (13-15).

This review will focus on the clinical role of pulsed Doppler echocardiography and pulsed tissue Doppler imaging to assess noninvasively the hemodynamic relationship between the LA and LV. In addition, this review will summarize the evidence supporting

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the use of these techniques to characterize the pathophysiology of diastolic LV dysfunction.

PULSED DOPPLER ECHOCARDIOGRAPHY

Transmitral flow (TMF) velocity

Diastole can be divided into four discrete phases: isovolumic relaxation, rapid filling, slow filling and atrial contraction (16). In a normal heart, LV relaxation begins during mid-systole and continues until the nadir of LV pressure decay in early diastole. In the diseased heart, LV relaxation abnormalities occur early, often preceding systolic dysfunction, resulting in a decrease in early diastolic filling and a compensatory increase in filling during atrial contraction. Diastolic filling is the period during which the LV fills with blood from the LA, and coincides with the period from the onset of mitral valve opening to mitral valve closure. Therefore, TMF velocity measurements are useful in evaluating LV diastolic relaxation and filling.

The TMF velocity pattern can be recorded by placing the sample volume at the tip of mitral valve leaflets in the LV long axis view using either transthoracic or transesophageal echocardiography.

In a normal subject in sinus rhythm, TMF velocity has a characteristic biphasic pattern. The two distinct peaks, representing early diastolic (E) and atrial systolic (A) velocity waves, can be clearly identified. A normal TMF velocity pattern is characterized by a short duration of early diastolic velocity phase, a rapid descent of the early diastolic flow velocity to baseline (shortening of the deceleration time), and a ratio of the peak early diastolic to the peak atrial systolic velocity ($E/A > 1$) (Fig.1, left). However, a decrease in the peak early diastolic velocity and prolongation in its deceleration time is associated with a compensatory increase in the peak atrial systolic velocity ($E/A < 1$, "relaxation failure") in patients with an impaired LV relaxation and a mildly to moderately elevated LV end-diastolic pressure or filling pressure (Fig.1, middle). These patients probably have an effective increase in LV volume during atrial contraction. Also, in the absence of underlying heart disease, an $E/A < 1$ can be observed with normal aging (17). Furthermore, in patients with markedly elevated LV end-diastolic pressures, the peak early diastolic velocity remains normal with a shortening in its deceleration time. In addition, the peak atrial systolic velocity is normal or depressed, resulting in a "pseudonormalization" ($E/A > 1$)

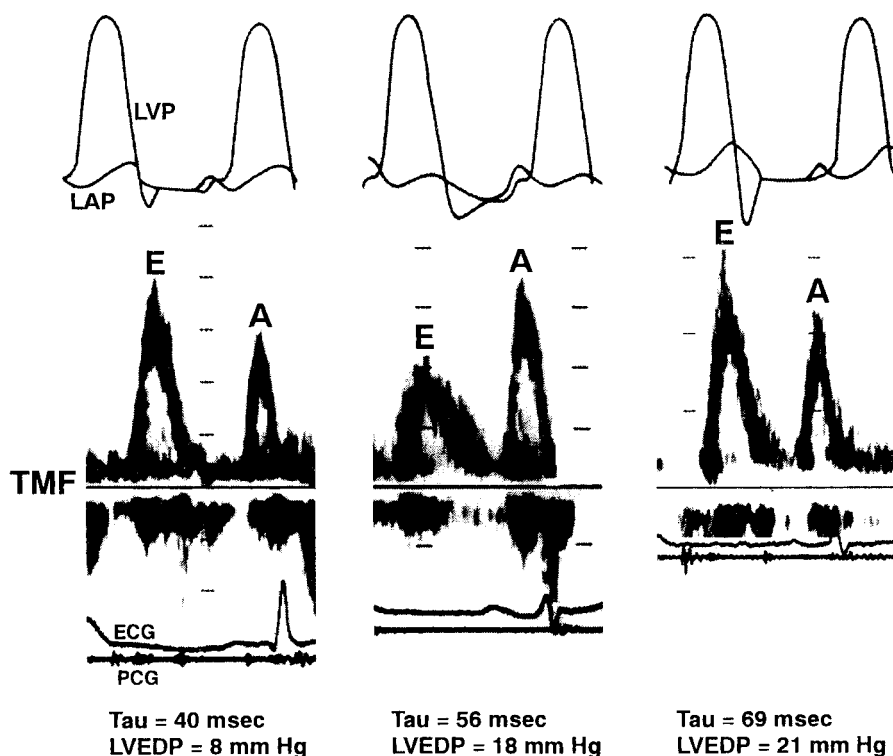


Fig.1. Transmitral flow (TMF) velocities recorded from a transthoracic approach simultaneously with left ventricular (LV) and left atrial (LA) pressure curves in a normal subject (left), and two patients with impaired relaxation (middle) and with markedly elevated LV end-diastolic pressure (right). Note the relation of the LV-LA pressure gradient to TMF velocity in these three conditions. E : peak early diastolic TMF velocity, A : peak atrial systolic TMF velocity, LVP : left ventricular pressure curve, LAP : left atrial pressure curve, Tau : time constant of LV pressure decay during isovolumic diastole, LVEDP : left ventricular end-diastolic pressure, ECG : electrocardiogram, PCG : phonocardiogram.

or "restrictive" ($E/A > 2$) velocity pattern (18, 19) (Fig.1, right).

Based on the above information, TMF velocity patterns are influenced by LA pressure, rate of LV relaxation, diastolic suction and the compliance of both the LA and LV. Recent studies have focused on distinguishing between the normal pattern and the "pseudonormalization" or "restrictive" pattern (20-25).

Pulmonary venous flow (PVF) velocity

The LA serves as a pump during active atrial contraction, a blood reservoir during ventricular systole, and a conduit for blood flow from the pulmonary veins into the LV during early to mid-diastole (26-28). Therefore, LA hemodynamic abnormalities can be determined by analyzing PVF and LAAF velocities. The PVF velocity can be measured by setting the sample volume within 1 to 2 cm of the junction of the left superior pulmonary vein with the LA using transesophageal echocardiography. Color flow imaging is used to obtain an ultrasound beam direction that is as parallel as possible to the venous flow. The flow velocity pattern in sinus rhythm is composed of a five-peak waveform consisting of three forward waves (first and second systolic and early to mid-diastolic waves) and two reverse waves (early systolic and atrial systolic waves) (Fig.2, left).

The first systolic forward wave (PVS_1) is believed to be caused by active relaxation of the LA (29, 30). Therefore, this wave disappears because of a lack of active LA relaxation in patients with atrial fibrillation, and also is markedly decreased in some patients with cardiac amyloidosis or dilated cardiomyopathy. These findings suggest that impaired active LA relaxation is caused by LA myocardial failure. The second systolic forward (PVS_2) and early to mid-diastolic forward (PVD) waves are represented by the X and Y descents of the LA pressure tracing, respectively. The PVS_2 reflects the reservoir function of the LA, and is determined by many factors, such as changes in systolic mitral annular motion caused by systolic LV dysfunction (31), mitral regurgitation (32, 33), changes in preload (34), and abnormal LA pressure and compliance (35-37). The PVD is believed to be related to LV filling during early diastole (conduit function). Therefore, PVD velocity changes in parallel with changes in the early diastolic TMF velocity (E).

A distinct reverse wave during early systole (PVC) is frequently observed in the presence of an elevated LA pressure, such as in the setting of mitral stenosis

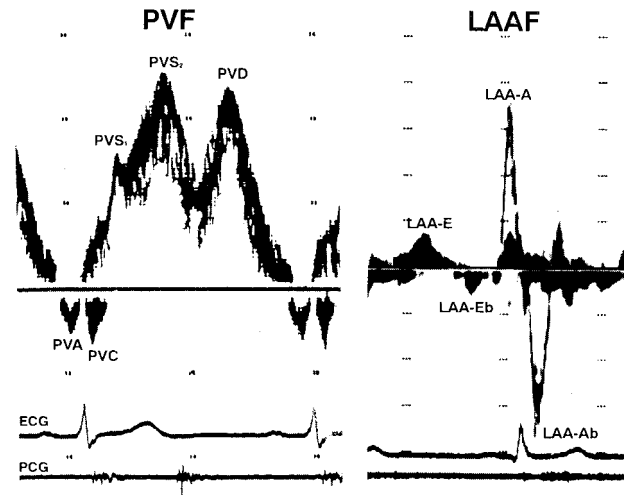


Fig. 2 . Pulmonary venous flow (PVF, left) and left atrial appendage flow (LAAF, right) velocities recorded from a transesophageal approach in normal subjects in sinus rhythm. PVC : peak early systolic reverse PVF velocity, PVA : peak atrial systolic reverse PVF velocity, PVS_1 : peak first systolic forward PVF velocity, PVS_2 : peak second systolic forward PVF velocity, PVD : peak early to mid-diastolic forward PVF velocity, LAA-E : peak early diastolic forward LAAF velocity, LAA-Eb : peak early diastolic reverse LAAF velocity, LAA-A : peak late emptying forward LAAF velocity, LAA-Ab : peak late filling reverse LAAF velocity, ECG : electrocardiogram, PCG : phonocardiogram.

or LA myxoma (38-41). The jugular C wave is attributed to the ballooning of the tricuspid valve toward the right atrium, combined with the end-diastolic closure of the tricuspid valve. The PVC develops in the presence of elevated LA pressure during closure of the mitral valve, resulting in regurgitant flow from the LA into the pulmonary veins, where resistance is lower. Therefore, this reverse wave is usually not observed in patients with a normal LA pressure. The atrial systolic reverse wave (PVA) is believed to be due to reflux flow into the pulmonary veins during LA contraction. In addition, the PVA changes in conjunction with changes in the atrial systolic TMF forward wave (A). Therefore, the PVA also disappears because of a lack of active LA contraction in patients with atrial fibrillation. The ventricular filling during atrial contraction depends on the LV pressure at which contraction begins, with less filling occurring in patients with a higher LV end-diastolic pressure (42, 43). However, LA myocardial contractility may also influence LV filling velocity in addition to LV compliance during end-diastole (44-46). Therefore, it is only by examining both the TMF and PVF velocity patterns that important information on these factors can be gained.

Left atrial appendage flow (LAAF) velocity

The LAA is a blind sac, and its orifice into the

LA main chamber is narrow. The LAAF velocity pattern can be measured by the pulsed Doppler method with a sample volume placed 1 cm from the LAA orifice on a transverse transesophageal view that includes the LA main chamber and appendage. The LAAF velocity pattern during sinus rhythm reveals a quadriphasic pattern consisting of early emptying and filling waves (LAA-E and -Eb, respectively), as well as late emptying and filling waves (LAA-A and -Ab, respectively) (Fig.2, right). The early emptying and filling waves are thought to be produced by LV relaxation and elastic recoil of the LAA, respectively. The late emptying and filling waves are thought to be produced by active contraction and relaxation of the LAA, respectively (47, 48). It is therefore likely that the peak of each flow velocity changes depending on LV relaxation or LAA contractility. In patients with atrial fibrillation, the LAAF velocity pattern has an irregular sawtooth waveform without the late emptying and filling waves.

Detailed examination of the LA main chamber and LAA has facilitated the detection of small thrombi in the LAA by transesophageal echocardiography (49, 50). In addition, a study of the LAAF velocity patterns obtained using the pulsed Doppler method has demonstrated thrombus formation in the LAA not only in patients with atrial fibrillation but also in patients in sinus rhythm with decreased peak LAAF velocities (51). Because the LAA communicates with the LA main chamber, and is located between the LV and the pulmonary veins, it is possible that LAAF velocities reflect hemodynamic changes for the left side of the heart. Specifically, LAAF velocities may reflect LA reservoir function in the presence of LA pressure and/or volume overload (52-54) or stunning immediately after cardioversion (55, 56). In addition, LAAF velocity may predict successful cardioversion of atrial fibrillation (57).

PULSED TISSUE DOPPLER IMAGING

The quantitative analysis of segmental wall motion by M-mode and two-dimensional echocardiography has previously been limited to the measurement of epicardial and endocardial edge excursion throughout the cardiac cycle. However, direct determination of myocardial velocity may be a more sensitive index of LV myocardial performance. Tissue Doppler imaging was recently developed as a modification of color Doppler imaging (13-15). Because the ventricular wall motion velocity is much lower than

the intracardiac blood flow velocity, the frequency shift for ventricular wall motion is also low. Moreover, because the amplitude of Doppler signals derived from myocardial tissue is about 40 dB higher than that derived from blood flow, isolated wall motion velocities can be measured by bypassing the high-pass filter that eliminates low amplitude Doppler shifts. Therefore, this new imaging method has the potential to evaluate segmental systolic and diastolic LV function.

LV wall motion velocities along the short axis are determined in the parasternal LV long axis echocardiogram (58-60), and the LV wall and mitral annulus motion velocities along the long axis are measured in the apical LV long axis echocardiogram (61-64) based on the pulsed Doppler method (Fig.3). According to histologic studies (65), it is well known that the LV myocardium consists of circumferential fibers in the mid-wall and longitudinal fibers in the subendocardial and subepicardial walls, and that systolic LV function reflects the sum of the contractions of these fibers. Pulsed tissue Doppler measurements provide important information regarding LV myocardial function not only along the short axis but also along the long axis.

In a normal subject, systolic LV wall motion velocity consists of two components, the first systolic wave (Sw_1) and the second systolic wave (Sw_2). Normally, the peak Sw_1 along the long axis is markedly greater than either the peak Sw_2 along the long axis or the peaks Sw_1 and Sw_2 along the short axis. The shortening of longitudinal fibers occurs before the shortening of circumferential fibers during early systole (66). As a result, the LV dimension along the short axis transiently increases during the isovolumic phase of contraction, and the LV cavity becomes more spherical (67). The peak of Sw_1 along the long axis almost coincides with the peak dP/dt of LV pressure curve. Therefore, the peak Sw_1 along the long axis is a more sensitive parameter for evaluating LV myocardial contractility (68).

In a normal subject, the diastolic motion velocity of the LV wall and mitral annulus both consists of two components, the early diastolic wave (Ew) and the atrial systolic wave (Aw) (58, 59). These flow velocities change in parallel with changes in the early diastolic (E) and atrial systolic (A) TMF velocities, respectively, in normal subjects and most patients. However, both the variables between the TMF and LV wall motion velocities indicate a difference in waveform by loading condition, par-

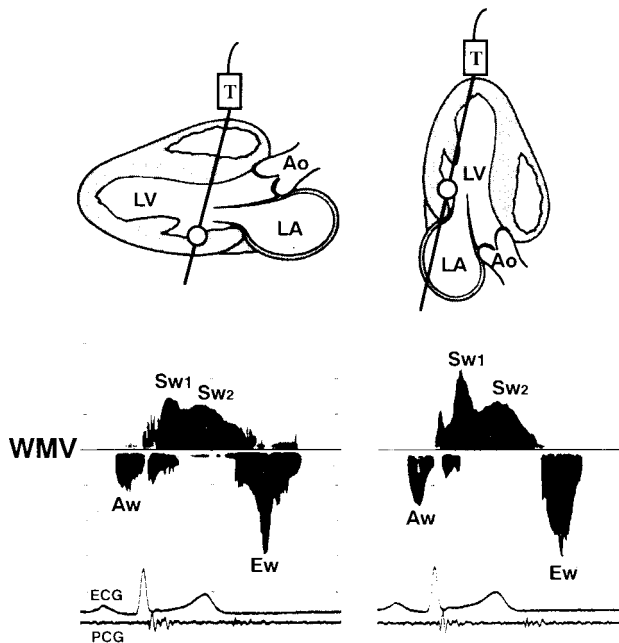


Fig.3. Measurement methods for left ventricular (LV) posterior wall motion velocities using pulsed tissue Doppler imaging. Two sample volumes (white circles) are set at the endocardial portions of the middle sites of the LV posterior wall in the parasternal (top, left) and apical (top, right) two-dimensional long axis echocardiograms of the LV. The bottom panel indicates the motion velocity patterns of the LV posterior wall in a normal subject in sinus rhythm. The peak velocity of the first systolic wave (Sw₁) along the long axis is markedly greater compared to that along the short axis and the peak velocities of the second systolic wave (Sw₂) along the short and long axes. T : transducer, LA : left atrium, Ao : ascending aorta, WMV : wall motion velocity, Ew : peak early diastolic velocity of the LV posterior wall, Aw : peak atrial systolic velocity of the LV posterior wall, ECG : electrocardiogram, PCG : phonocardiogram.

ticularly changes in preload (58, 69). In addition, pulsed tissue Doppler variables reveal a characteristic pattern rather than TMF velocity variables in patients with constrictive pericarditis (63).

CLINICAL IMPLICATIONS

Hypertrophied hearts

The TMF velocity pattern has been used to assess LV diastolic properties, and to evaluate the improvement of LV diastolic dysfunction after medical treatment (70, 71), because this method is not influenced by LV morphology or wall motion abnormalities. Hypertrophied hearts, especially hypertrophic cardiomyopathy, is characterized by impaired LV diastolic function due to an increase in LV wall thickness. However, the severity of LV diastolic dysfunction in this disease is not necessarily associated with the location or the degree of LV wall thickening. Rather, it primarily depends on the

severity of myocardial fiber disarray and fibrosis (72).

The TMF velocity pattern can vary in patients with hypertrophied hearts under different hemodynamic states (Fig.4). A decrease in the peak early diastolic velocity (E), prolongation of the E wave deceleration time, and a compensatory increase in the peak atrial systolic velocity ($E/A < 1$, "relaxation failure") are common findings in the setting of LV hypertrophy (Fig.4, middle). This pattern is thought to reflect most accurately impairment of LV relaxation, abnormal LV filling from early to mid-diastole, and a preserved atrial kick during atrial contraction. However, it is inappropriate to discuss differences in LV diastolic function between LV hypertrophied patients with a normal TMF velocity pattern ($E/A > 1$) and with a "pseudonormalization" pattern ($E/A > 1$) on the basis of TMF velocity alone (73, 74).

In patients with a "pseudonormalization" pattern (Fig.4, right), the relaxation ability of the LV is markedly decreased and the pressure gradient between the LA and LV is reversed during early diastole, causing early termination of rapid LV filling. Moreover, the LV end-diastolic pressure is markedly increased, causing normal or no increased peak atrial systolic TMF velocities. As a result, regurgitation into the low-pressure pulmonary veins is augmented with a consequent increase of peak atrial systolic PVF velocity (PVA), whereas PVA is normal in velocity in patients with a normal TMF velocity pattern (29, 75) (Fig.4, left). This induces an afterload mismatch for the LA and may explain the possibility of congestive heart failure in the setting of marked LV diastolic dysfunction despite normal LV systolic pump function (1-4, 76). Therefore, a comprehensive evaluation of both atrial systolic TMF and PVF velocities provides important information regarding LA pressure and volume changes during atrial contraction in patients with LV hypertrophy (77).

In patients with hypertrophic cardiomyopathy and asymmetric septal hypertrophy, the ventricular septum frequently becomes hypokinetic or akinetic as hypertrophy increases. In addition, the posterior wall may have normal or hyperkinetic motion in order to compensate for the abnormal ventricular septal motion using M-mode echocardiography. However, the peak systolic velocity of the LV posterior wall determined by pulsed tissue Doppler imaging is decreased in some patients despite the absence of hypertrophy (59). This result

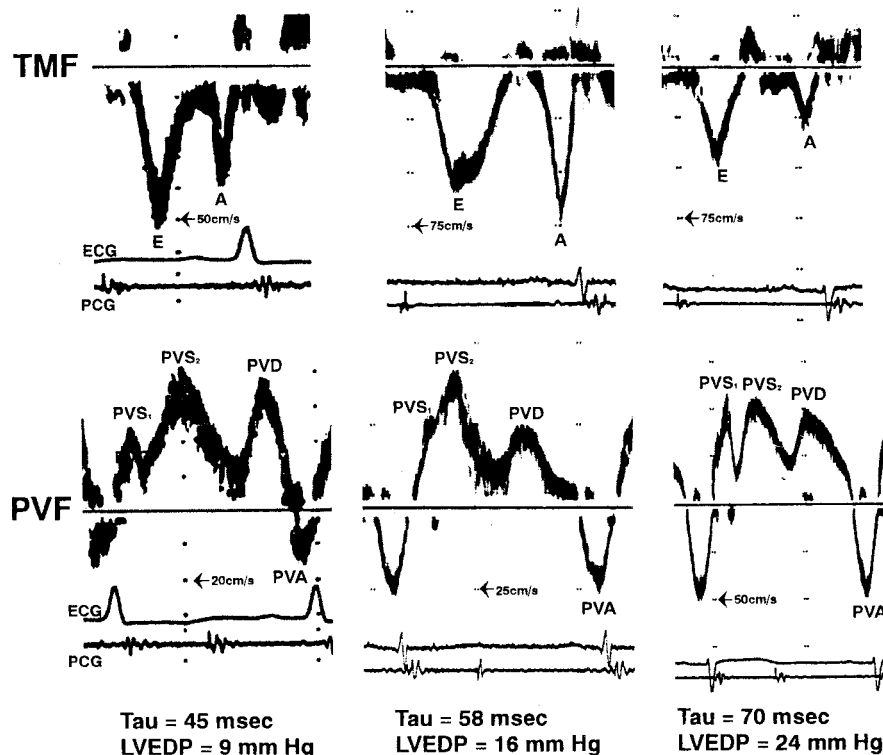


Fig.4. Transmitral flow (TMF, top) and pulmonary venous flow (PVF, bottom) velocities recorded from a transesophageal approach in three representative patients with hypertrophic cardiomyopathy. In the patient with impaired left ventricular relaxation (middle), the ratio of the peak early diastolic to the peak atrial systolic TMF velocity (E/A) is lower than one, and the peak atrial systolic PVF velocity (PVA) is slightly increased despite the decrease in the peak early to mid-diastolic PVF velocity (PVD). Differentiation of the patient with a "pseudonormalization" TMF pattern (E/A>1) (right) from the patient with a normal TMF pattern (E/A>1) (left) is difficult by TMF alone. However, the PVA is markedly increased in the patient with a "pseudonormalization" pattern compared to the patient with a normal pattern. PVS₁: peak first systolic forward PVF velocity, PVS₂: peak second systolic forward PVF velocity, Tau: time constant of LV pressure decay during isovolumic diastole, LVEDP: left ventricular end-diastolic pressure, ECG: electrocardiogram, PCG: phonocardiogram.

suggests that myocardial damage in patients with asymmetric septal hypertrophy also occurs in the nonhypertrophied LV posterior wall (78).

Dilated hearts

Abnormalities of diastolic LV function have been described in patients with heart failure in the setting of systolic dysfunction. In such patients, a greater percentage of the stroke volume enters the LV in the first third of diastole, resulting in a "pseudonormalization" (E/A>1) (Fig.5, middle) or "restrictive" (E/A>2) (Fig.5, right) pattern. These characteristic LV filling patterns are often seen in patients with coronary heart disease, dilated cardiomyopathy, or cardiac amyloidosis. Previous data from patients with congestive heart failure indicate that a "restrictive" TMF velocity pattern may be related to advanced New York Heart Association functional class (79), and increased mortality (80-82). Therefore, it is very important to determine LV diastolic function based on TMF and PVF velocities in patients with dilated failing hearts.

It is well known that the Frank-Starling mechanism acts in the LA as well as in the LV (83-85). In patients with mild left heart failure, or under conditions in which the LV end-diastolic pressure is not markedly elevated, cardiac output can be maintained by use of this mechanism. Because the preload reserve force is preserved to some degree in the LA in this setting, LA contraction is augmented compensatorily even by a slight elevation of afterload against the LA ("relaxation failure" pattern of TMF velocity) (Fig.5, left). As a result, the ejection volume directed toward the LV does not significantly decrease.

In general, LA afterload mismatching occurs when venous return (preload) is insufficient to compensate for an increased afterload, or when the Frank-Starling mechanism cannot compensate for increases in afterload. The LA gradually dilates as left heart failure progresses, and when the preload reserve force is maximally utilized, the pump properties of the LA are depressed even with slight elevations in LA pressure. As a result, the

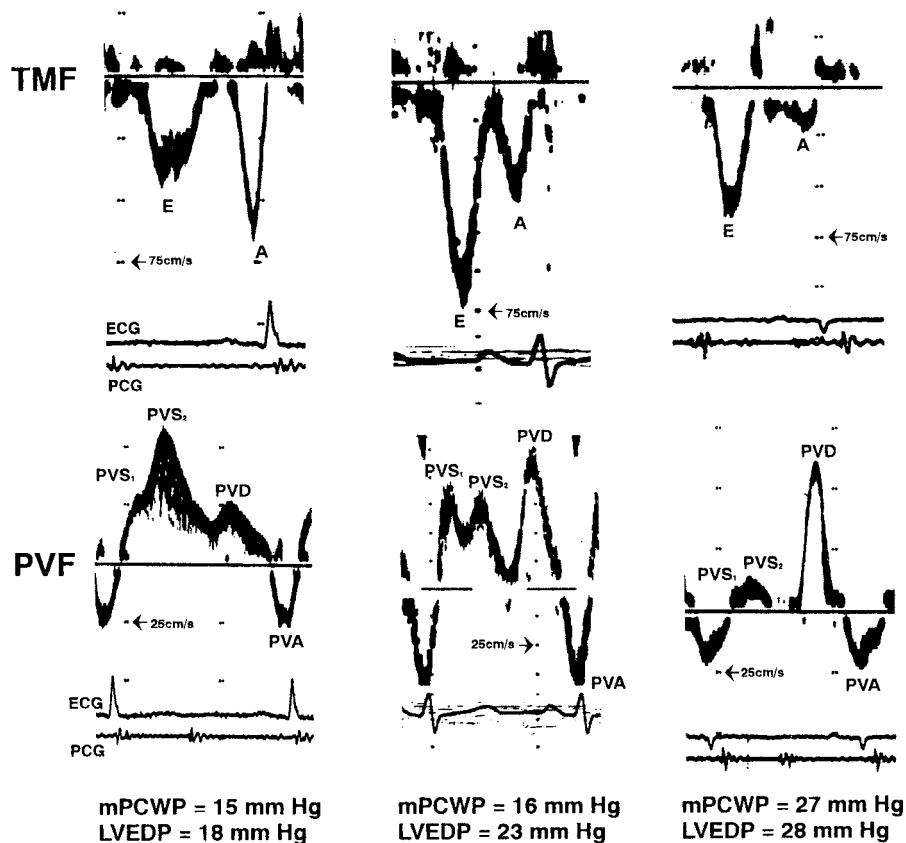


Fig.5. Transmitral flow (TMF, top) and pulmonary venous flow (PVF, bottom) velocities recorded from a transesophageal approach in three representative patients with dilated failing hearts. Impaired left ventricular relaxation pattern of the TMF [ratio of the peak early diastolic to the peak atrial systolic velocity (E/A) <1] (left) is well seen in patients with mild to moderate increase in left atrial or left ventricular end-diastolic pressures (LVEDP). In the patient with a "pseudonormalization" TMF pattern ($E/A >1$) (middle), PVF shows an augmentation of the peak atrial systolic velocity (PVA), suggesting no increase in left atrial pressure corresponding to the markedly increased LVEDP. However, both the pressures are markedly increased in the patient with a "restrictive" TMF pattern ($E/A >2$) (right), resulting in the decrease in both peak atrial systolic TMF and PVF velocities (A and PVA, respectively). In addition, the peak second systolic forward PVF velocity (PVS₂) also is decreased due to markedly increased left atrial pressure in the patient with a "restrictive" pattern. PVS₁: peak first systolic forward PVF velocity, PVD: peak early to mid-diastolic forward PVF velocity, mPCWP: mean pulmonary capillary wedge pressure, ECG: electrocardiogram, PCG: phonocardiogram.

TMF velocity gradually changes from a "relaxation failure" ($E/A <1$) pattern to a "pseudonormalization" ($E/A >1$) or "restrictive" ($E/A >2$) pattern in the setting of elevated LV end-diastolic pressure. However, patients with a "pseudonormalization" pattern do not always have an elevation of LA pressure corresponding to the markedly elevated LV end-diastolic pressure. It is known that the pulmonary venous system has a lower resistance than the LV during ventricular diastole (75). When the LV end-diastolic pressure is markedly elevated, as in patients with a "pseudonormalization" pattern, blood in the LA flows toward the pulmonary veins rather than toward the LV because of the increase in LA contractility, unless LA myocardial damage has occurred (44-46).

In patients with a "restrictive" pattern, on the other hand, LV end-diastolic pressure and LA pressure are markedly elevated, suggesting that both

pressures are in competition (86). With the pulmonary veins and the LV acting as afterload circuits for the LA, marked increases in LA or pulmonary venous pressure decrease retrograde blood flow from the LA to the pulmonary veins. Further, marked elevation of the LV end-diastolic pressure decreases blood flow from the LA to the LV during atrial contraction. As a result, these changes decrease both the peak atrial systolic TMF and PVF velocities. Although this hemodynamic abnormality represents LA afterload mismatch arising from the increased LA pressure and/or increased pulmonary vascular resistance caused by pulmonary congestion in the setting of chronic heart failure (87), occult LA myocardial failure may also cause this condition (29, 44-46). The presence of LA myocardial failure should be suspected in patients with no improvement in their peak atrial systolic TMF and/or PVF velocity

patterns after decreasing the LA pressure and LV end-diastolic pressure through medical treatment of their heart failure. A “pseudonormalization” or “restrictive” pattern and “relaxation failure” pattern in dilated hearts may be readily interchangeable by altering preload conditions. Therefore, changes in the TMF and PVF velocity patterns during changes in preload can be used to determine the hemodynamic severity of disease (34, 76, 88). The PVF velocity pattern shows retrograde flow from the LA to the pulmonary veins not only during atrial systole but also during mid-diastole in the presence of markedly elevated LA pressures (89). In addition, the peak systolic (PVS₂) and early to mid-diastolic (PVD) PVF velocities can be used to evaluate the LA pressure (35, 90).

The TMF and PVF velocity variables are influenced by age, loading conditions and other factors. The difference in duration of the peak atrial systolic PVF and TMF velocities has recently been shown to relate to the increase in LV pressure during atrial contraction as well as the LV end-diastolic pressure (91). Patients with higher LV filling pressures have a shorter duration of the peak atrial systolic TMF velocity and a longer duration of the peak atrial systolic PVF velocity. As a result, their difference in duration is greater. Therefore, this variable may be used to identify increased LV diastolic pressures, and may be less age dependent than the forementioned variables of TMF and PVF velocities.

The blood flow from the LA to the LV during early diastole is controlled by active relaxation of the LV myocardium and by ventricular filling, which is determined by the pressure difference between the LA and the LV after the opening of the mitral valve. LV myocardial fibers begin to relax during the ejection period. However, the equalization of the LV and aortic pressures is considered the onset of the isovolumic relaxation period. When LV relaxation is impaired, LV filling is maintained by the augmentation of LA contraction. However, if the LA contraction is not sufficient, LV filling requires an increase in LA pressure, resulting in pulmonary congestion (92). The advent of TMF and PVF velocity analysis has provided a noninvasive means to evaluate LV diastolic function. However, many recent studies have emphasized that “pseudonormalization” or “restrictive” patterns of TMF velocity mask abnormal LV relaxation by changing the waveform, including shortening the isovolumic relaxation time, shortening the rapid filling time and altering the

E/A ($E/A > 1$ or $E/A > 2$). Therefore, LV relaxation abnormalities may not be detected from TMF velocity patterns using pulsed Doppler echocardiography in patients with markedly elevated LV end-diastolic pressures.

Recent studies (58, 93) have demonstrated that the period from the aortic component of the second heart sound to the onset or peak of the early diastolic wave (Ew) determined from the LV wall motion velocity recorded by pulsed tissue Doppler imaging correlates well with the time constant for the LV pressure decay at isovolumic diastole (τ) determined by cardiac catheterization in all patients, including patients with markedly elevated LV end-diastolic pressures. Interestingly, this time interval is equal to or shorter than the isovolumic relaxation time in all normal subjects and in some patients with a “relaxation failure” TMF velocity pattern ($E/A < 1$) (Fig. 6, left). This finding suggests that LV wall expansion starts at the same time as, or earlier than, LV filling during early diastole, and that elastic recoil of the LV myocardium promotes LV filling. However, in some patients with an $E/A < 1$ and in all patients with a “pseudonormalization” or “restrictive” pattern for the TMF velocity, LV filling begins during active LA relaxation (Fig. 6, middle and right). Further, this tendency is more pronounced in the latter group of patients. This finding suggests that a marked increase in LA pressure causes the mitral valve to open earlier in the process of a delay in the elastic recoil of the LV wall, and that passive expansion of the LV may be caused by LV filling. This phenomenon causes a rapid increase in LV pressure, leading to a decrease in the pressure difference between the LA and LV, and early termination of the rapid filling period. The temporal relationship between LV wall motion and TMF velocities varies with disease severity. Assessment of these parameters may be useful for evaluating LV hemodynamic abnormalities during early diastole.

Another novel technique is measurement of the velocity of propagation across the mitral valve based on color Doppler M-mode echocardiography (94). The slope of the color Doppler M-mode early diastolic wave reflects the propagation velocity, which is distinct from the peak early diastolic TMF velocity (E). Typically, the propagation velocity is lower than the peak early diastolic (E) velocity in patients with a “pseudonormalization” pattern, due to the phenomenon of vortex shedding by which the E wave propagates into the LV. The velocity of propagation

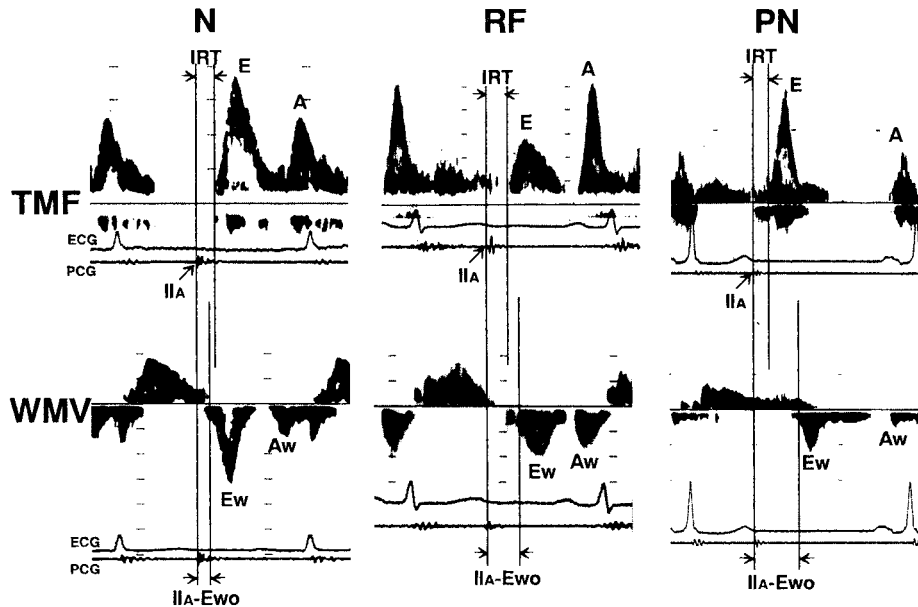


Fig.6. Transmittal flow (TMF, top) and left ventricular posterior wall motion (WMV, bottom) velocities recorded from a transthoracic approach in a normal subject (N), and 2 patients with an impaired left ventricular relaxation (RF) and with a markedly increased left ventricular end-diastolic pressure (PN). In the N (left), the time from the aortic component of the second heart sound to the onset of the early diastolic wave of the left ventricular posterior wall motion velocity (IIA-Ewo) is shorter than the isovolumic relaxation time (IRT). However, the IIA-Ewo is longer than the IRT in the patients with a "relaxation failure" TMF pattern (middle) and with a "pseudonormalization" TMF pattern (right), especially in the latter patient. E : peak early diastolic TMF velocity, A : peak atrial systolic TMF velocity, Ew : peak early diastolic velocity of the left ventricular posterior wall, Aw : peak atrial systolic velocity of the left ventricular posterior wall, ECG : electrocardiogram, PCG : phonocardiogram.

is linearly related to LA pressure irrespective of preload.

Atrial fibrillation (AF)

The R-R interval is always irregular in patients with atrial fibrillation (AF), thus AF is called an absolute arrhythmia. This arrhythmia provides a unique opportunity for studying the complex interplay between LV ejection and filling over a large number of randomly associated cycle lengths, free from the influence of other changes in physiological state. In patients with AF, the atrial systolic wave is absent from both the TMF and PVF velocities. As a result, one cannot estimate the LV filling pressure or end-diastolic pressure using the E/A for the TMF velocity or the peak atrial systolic retrograde velocity for the PVF, (95). However, LV function and filling curve can be determined based on the Frank-Starling relationship because the blood volume flowing into the LV (preload) varies with every cardiac cycle in the setting of AF.

The early systolic reversal wave of the PVF velocity pattern (PVC) is augmented in patients with mitral stenosis (Fig.7, middle), LA myxoma or dilated failing hearts (Fig.7 bottom) compared with patients with isolated AF (Fig.7, top) or normal subjects in sinus rhythm, in whom normal LA pressures

and pliable mitral valves are found (41). A significant negative correlation exists between the peak PVC and the LA pressure during closure of the mitral valve and the preceding R-R interval in patients with mitral stenosis. In addition, the slopes of these relationships are lower in patients with more severe mitral stenosis, having high LA pressures and poor mitral valve pliability, than in patients with mild mitral stenosis. In contrast, a significant positive correlation exists between the peak second systolic PVF velocity (PVS_2) and the preceding R-R interval in patients with mitral stenosis (Fig.7, middle). This correlation is explained by beat-to-beat changes in preload, consistent with the Frank-Starling mechanism in the LA. When the R-R interval is relatively long, the LV fills sufficiently and the LA is almost completely emptied. Therefore, blood flow from the pulmonary veins into the LA increases during the next ventricular systole, and consequently, PVS_2 is enhanced. However, when the R-R interval is relatively short, the LV does not fill sufficiently, and blood remains in the LA. As a result, the PVS_2 is decreased. In patients with isolated AF, the inflow from the LA to the LV is almost completed during the rapid filling phase, and the PVS_2 is constant during each cardiac cycle (Fig.7, top).

Generally, the mortality of patients with underlying

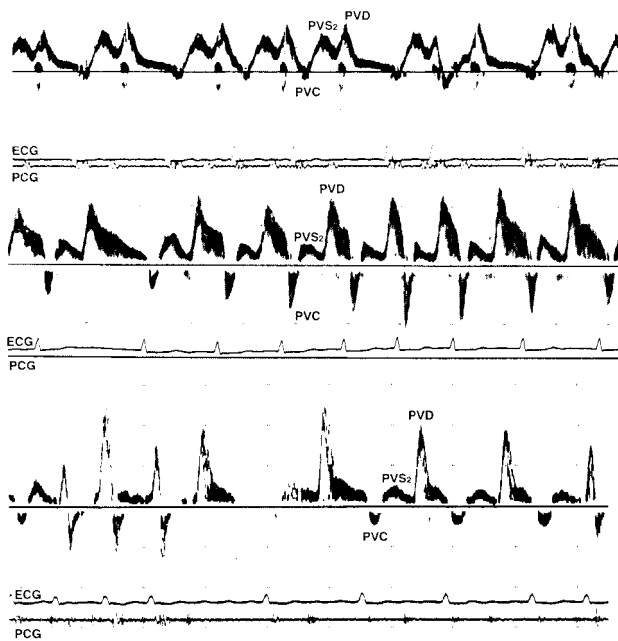


Fig.7. Pulmonary venous flow velocities recorded from a transesophageal approach in three representative patients with atrial fibrillation. The peak early systolic reverse velocities (PVCs) are markedly greater in two patients with mitral stenosis (middle) and with dilated failing heart (bottom) than in the patient with isolated atrial fibrillation (top). In the patient with mitral stenosis, the PVCs vary inversely, and the peak second systolic forward velocities (PVS₂s) vary directly with the preceding R-R intervals. However, the PVS₂s show no significant variation with the preceding R-R intervals in the patient with isolated atrial fibrillation and with dilated failing heart and markedly increased left atrial pressure (mean pulmonary capillary wedge pressure=20 mm Hg). PVD : peak early to mid-diastolic forward velocity, ECG : electrocardiogram, PCG : phonocardiogram.

heart disease and AF is higher than in patients with isolated AF. In patients in sinus rhythm with mitral stenosis, if there is long-term LA enlargement and elevated LA pressures, the LA will become fatigued, and LA function will gradually decrease. In this setting, the loss of the atrial kick caused by AF induces pulmonary congestion by decreasing the PVS₂ and reduces cardiac output because of a lack of the peak atrial systolic TMF velocity and increase in heart rate. Therefore, it is important to evaluate the LA contribution to LV filling in patients with mitral stenosis and sinus rhythm (96) and to predict for successful cardioversion in patients with AF (57).

LA systolic function in patients with stiff and failing hearts is essential for adequate LV filling during ventricular diastole (97). If AF occurs in these patients, the loss of an effective atrial contribution may result in a decrease in LV filling, which can markedly affect LV function. In patients with isolated AF, cardiac output is not significantly affected even when atrial pump function is lost because the reservoir

and conduit functions of the LA are maintained. However, loss of atrial contraction due to AF will significantly affect LV function under conditions in which the LA reservoir function is decreased, as in some patients with hypertrophic cardiomyopathy (85). In these patients, the PVS₂ correlates directly with the preceding R-R interval, and the cardiac output is probably maintained by the LA Frank-Starling mechanism because the relatively high pulmonary capillary wedge pressure acts to increase atrial preload (76). In many patients with a dilated failing heart, in whom the PVS₂ correlates directly with the preceding R-R interval, it is possible that the atrial Frank-Starling mechanism is also recruited, as in fore-mentioned patients with hypertrophic cardiomyopathy, and the slope of the relationship will be lower in patients with more severe LV dysfunction (98) (Fig.7, bottom). However, in patients with LA myopathy (44-46), the Frank-Starling mechanism can no longer be utilized effectively, which may contribute to a poorer prognosis in such patients.

LA mechanical contractility is severely impaired immediately after the electrical cardioversion of AF. This has been referred to as the "stunned LA" phenomenon (99). The atrial systolic waves of the TMF and PVF velocities, and the atrial systolic emptying wave of the LAAF velocity are thought to be due to active contraction of the LA main chamber and LAA, respectively. Further, the first systolic wave of the PVF velocity is thought to be caused by active relaxation of the LA main chamber (29, 30, 56). The values for these variables are markedly low immediately after cardioversion and increase gradually with time, suggesting stunning of the LA main chamber and LAA immediately after cardioversion, and recovery from myocardial stunning (30, 55, 56, 100) (Fig.8).

STUDY LIMITATIONS

Despite the advantages of evaluating LV diastolic function by pulsed Doppler echocardiography and pulsed tissue Doppler imaging, these modalities still have some limitations. First, LV diastolic filling is a complex phenomenon determined by multiple factors, including LV relaxation, intrinsic myocardial muscle properties and loading conditions of the LV. While pulsed Doppler measurements of TMF, PVF and LAAF velocities provide an assessment of LV diastolic performance, this technique

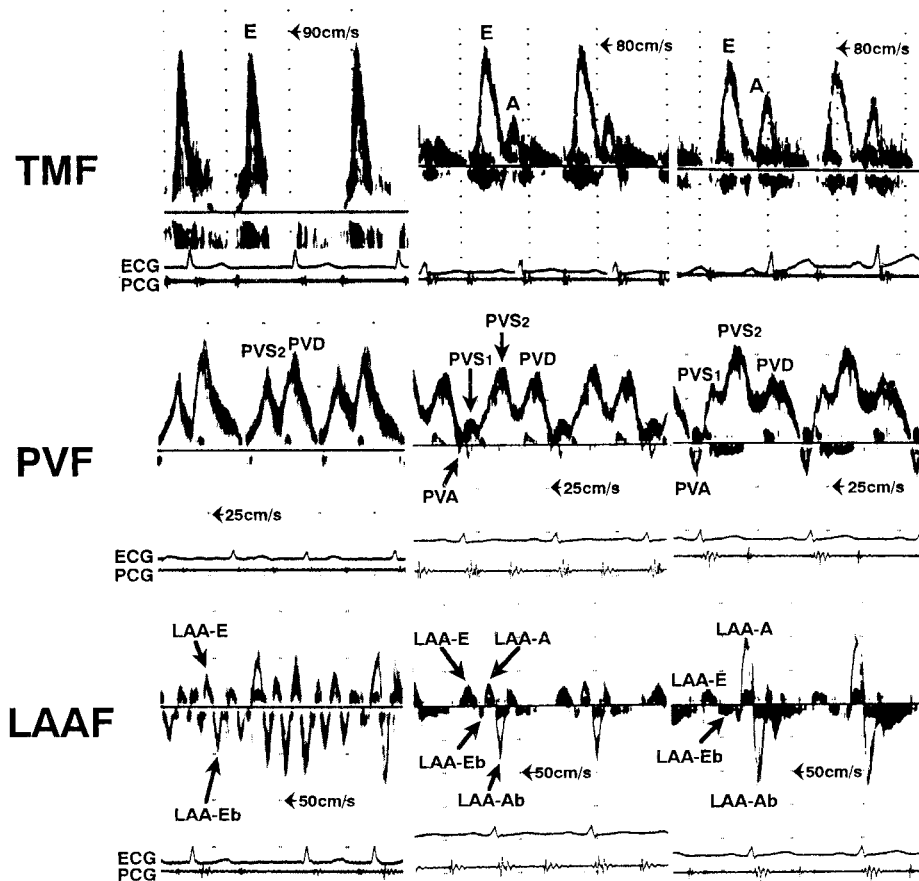


Fig.8. Changes in transmitral flow (TMF, top) velocity recorded from a transthoracic approach, pulmonary venous flow (PVF, middle) and left atrial appendage flow (LAAF, bottom) velocities recorded from a transesophageal approach before and after cardioversion in a patient with isolated atrial fibrillation. Before cardioversion of atrial fibrillation (left), note no peak atrial systolic TMF and PVF velocities (A and PVA, respectively), peak first systolic PVF velocity (PVS₁) and peak late emptying toward and filling reverse LAAF velocities (LAA-A and LAA-Ab, respectively). However, these peak velocities are slightly greater one week (right) than 24 hours (middle) after cardioversion. E : peak early diastolic TMF velocity, PVS₂ : peak second systolic forward PVF velocity, PVD : peak early to mid-diastolic forward PVF velocity, LAA-E : peak early diastolic forward LAAF velocity, LAA-Eb : peak early diastolic reverse LAAF velocity, ECG : electrocardiogram, PCG : phonocardiogram.

does not permit an independent estimate of these different determinants of diastolic function (7, 8, 25).

Second, pulsed tissue Doppler imaging in this study measures the motion velocity only at the endocardial portions of the LV wall and therefore cannot calculate the transmural velocity gradient. Consequently, disease-associated influences on the motion of the whole heart cannot be ruled out (14, 15). However, the motion velocity at the endocardial portion generally is significantly higher than that at the epicardial portion. Furthermore, the goal of this modality is not to obtain absolute values of the various parameters in patients with different conditions, but to determine differences between the patient groups and the normal subjects.

Third, in patients with regional LV asynergy, the evaluation of global LV diastolic abnormalities solely from the motion velocity of the posterior wall using pulsed tissue Doppler imaging will provide insufficient information (58, 59).

Finally, pulsed Doppler echocardiography or pulsed tissue Doppler imaging has intrinsic technical limitations. As in echocardiographic examination, it cannot accurately reflect blood flow or wall motion velocity, if the direction of the ultrasound beam is perpendicular or parallel to the blood flow or wall motion, respectively.

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